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Copper-Catalyzed Amination of Silyl Ketene Acetals with *N*-Chloroamines

Tomoya Miura,* Masao Morimoto, and Masahiro Murakami*

Department of Synthetic Chemistry and Biological Chemistry, Kyoto University,
Katsura, Kyoto 615-8510, Japan

tmiura@sbchem.kyoto-u.ac.jp; murakami@sbchem.kyoto-u.ac.jp

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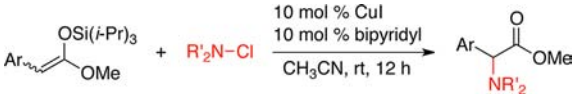
ABSTRACT



A copper(I)/2,2′-bipyridyl complex catalyzes an amination reaction of silyl ketene acetals with *N*-chloroamines, presenting a new preparative method of α-amino esters.

Amines intrinsically possess a nucleophilic property. Their nucleophilic substitution reactions present conventional preparative methods of substituted amines. Transition-metal-catalyzed cross-coupling reactions of aryl halides with amines are also powerful methods for the formation of C–N bonds.[1] An alternative pathway to substituted amines has recently become available by the use of electrophilic amination reagents together with nucleophilic organometallic species.[2] For example, Johnson and co-workers have reported their pioneering research on copper- and nickel-catalyzed amination reactions of diarylzinc compounds using *N*-hydroxyl(dialkyl)amine derivatives as the amination reagent.[2e,f] *N*-Chloroamines are also promising amination reagents with their easy availability[3] as well as high reactivity.[4] Jarvo and co-worker reported a nickel-catalyzed amination reaction of diarylzinc compounds with *N*-chloro(dialkyl)amines, which formed tertiary anilines.[2k] Similarly, secondary anilines are produced by the reaction of in situ-generated *N*-chloro(monoalkyl)amines with arylmagnesium reagents in the presence of an excess amount of titanium(IV) isopropoxide.[2l,5] Furthermore, transition-metal-catalyzed direct C–H amination reactions of aromatic compounds with *N*-chloro(dialkyl)amines have been developed by Miura,[6] Yu,[7] and Glorius.[8,9] It is also possible to introduce an amino group at the α-positions of carbonyl compounds by the reaction of their lithium enolates with *N*-chloroamines,[10,11] although the substrate scope is limited probably due to the strongly basic reaction conditions

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(1) For reviews, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Tasler, S.; Lipshutz, B. H. *J. Org. Chem.* **2003**, *68*, 1190. (c) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (d) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, 829. (e) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27.

(2) For reviews on transition-metal-catalyzed reactions of organometallic reagents with electrophilic nitrogen sources, see: (a) Narasaka, K.; Kitamura, M. *Eur. J. Org. Chem.* **2005**, 4505. (b) Barker, T. J.; Jarvo, E. R. *Synthesis* **2011**, 3954. For recent examples, see: (c) Tsutsui, H.; Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1997**, 317. (d) Erdik, E.; Daskapan, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3139. (e) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680. (f) Berman, A. M.; Johnson, J. S. *Synlett* **2005**, 1799. (g) Liu, S.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2007**, *9*, 1947. (h) He, C.; Chen, C.; Cheng, J.; Liu, C.; Liu, W.; Li, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 6414. (i) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918. (j) Zhang, Z.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 3005. (k) Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598. (l) Barker, T. J.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 8325. (m) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3642. (n) Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3953. (o) Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. *J. Am. Chem. Soc.* **2012**, *134*, 6571. (p) Xiao, Q.; Tian, L.; Tan, R.; Xia, Y.; Qiu, D.; Zhang, Y.; Wang, J. *Org. Lett.* **2012**, *14*, 4230. (q) Yan, X.; Chen, C.; Zhou, Y.; Xi, C. *Org. Lett.* **2012**, *14*, 4750. (r) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2012**, *77*, 617.

(3) *N*-Chloroamines are readily prepared by treatment of secondary amines with an aqueous solution of sodium hypochlorite or with *N*-chlorosuccinimide. (a) Broka, C. A.; Eng, K. K. *J. Org. Chem.* **1986**, *51*, 5043. (b) Zhong, Y.-L.; Zhou, H.; Gauthier, D. R., Jr.; Lee, J.; Askin, D.; Dolling, U. H.; Volante, R. P. *Tetrahedron Lett.* **2005**, *46*, 1099.

(4) For a review on reactions of *N*-chloroamines with other nucleophiles, see: Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337.

(5) For electrophilic aminations of Grignard reagents with *N*-chloro(dialkyl)amines, see: (a) Sinha, P.; Knochel, P. *Synlett* **2006**, 3304. (b) Hatakeyama, T.; Yoshimoto, Y.; Ghorai, S. K.; Nakamura, M. *Org. Lett.* **2010**, *12*, 1516.

(6) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900.

(7) Ng, K.-H.; Zhou, Z.; Yu, W.-Y. *Org. Lett.* **2012**, *14*, 272.

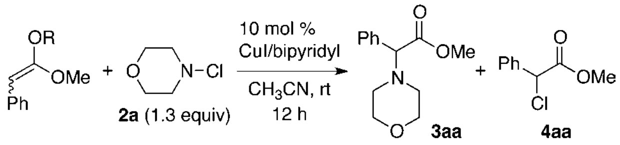
(8) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2012**, *14*, 656.

10.1021/ol302331k

as well as competing side reactions such as a chlorination reaction. We envisaged that an analogous amination reaction of carbonyl compounds would become feasible under milder conditions if it is assisted by transition-metal catalysts. Herein we report that a copper(I)/2,2′-bipyridyl complex successfully catalyzes an amination reaction of silyl ketene acetals with *N*-chloroamines to afford α-amino esters.

We initially attempted a direct amination reaction of methyl phenylacetate with *N*-chloromorpholine (**2a**, 1.3 equiv) in the presence of CuI (10 mol %) and 2,2′-bipyridyl (10 mol %). Various bases (2.0 equiv) such as NEt(*i*-Pr)$_2$, K$_2$CO$_3$, and K(O*t*-Bu) were examined, and the desired methyl 2-morpholino-2-phenylacetate (**3aa**) was formed in 6% (NMR) yield at best when K$_2$CO$_3$ was used. Then, methyl phenylacetate was replaced by its activated form, trimethylsilyl ketene acetal **1a** (*E*/*Z* = 76:24). An amination reaction proceeded in the absence of a base, and after 12 h, **3aa** was obtained in 39% yield together with methyl 2-chloro-2-phenylacetate (**4aa**, 29% yield) (Scheme 1).

Scheme 1. Effect of Silyl Group

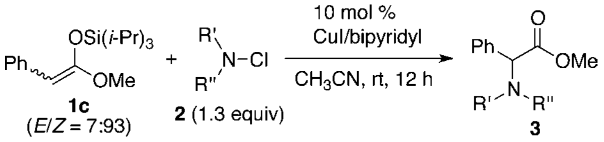


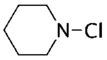
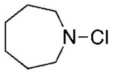
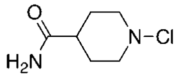
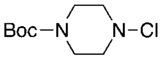
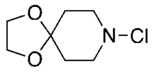
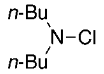
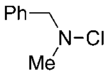
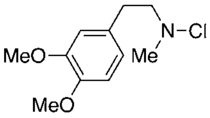
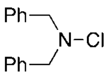
	3aa	4aa
1a (R = SiMe$_3$, *E*/*Z* = 76:24)	39%	29%
1b (R = Si(*t*-Bu)Me$_2$, *E*/*Z* = 85:15)	57%	20%
1c (R = Si(*i*-Pr)$_3$, *E*/*Z* = 82:18)	80%	10%
1c (R = Si(*i*-Pr)$_3$, *E*/*Z* = 7:93)	77%	8%

Other sterically bulkier silyl groups were examined, and **3aa** was obtained in 80% isolated yield when triisopropylsilyl ketene acetal **1c** (*E*/*Z* = 82:18) was employed. It seemed that bulkier silyl groups disfavored the formation of **4aa** to improve the yield of **3aa**. A similar result was observed with **1c** of an opposite *E*/*Z* ratio (7:93).[12,13] In the absence of a copper catalyst, only a small amount of **4aa** (5% yield) was obtained together with the recovered **1c** (95%).

Various *N*-chloroamines **2** were subjected to the amination reaction of **1c** (*E*/*Z* = 7:93) (Table 1). Cyclic *N*-chloroamines **2b**–**f** reacted smoothly to give the corresponding products **3cb**–**cf** in yields ranging from 60 to 83% (entries 1–5). Acyclic *N*-chloroamines **2g**–**i** were also competent amination reagents (entries 6–8). On the other hand, the reaction with *N*-chloro(dibenzyl)amine (**2j**) gave the product **3cj** in only 28% yield due to a competing chlorination reaction of **1c** (entry 9).

Table 1. Cu(I)-Catalyzed Amination Reaction of Silyl Ketene Acetal **1c** with Various *N*-Chloroamines **2b**–**j**[a]



entry	2		3	yield/%[b]
1		**2b**	**3cb**	82
2		**2c**	**3cc**	68
3		**2d**	**3cd**	60
4		**2e**	**3ce**	74
5		**2f**	**3cf**	83
6		**2g**	**3cg**	56[c]
7		**2h**	**3ch**	74
8		**2i**	**3ci**	73
9		**2j**	**3cj**	28[d]

[a] Conditions: **1c** (0.20 mmol), **2** (0.26 mmol), CuI (10 mol %), and 2,2′-bipyridyl (10 mol %) in CH$_3$CN (2 mL) at rt for 12 h, unless otherwise noted. [b] Isolated yields (averages of 2 runs). [c] Using 0.30 mmol of **2g**. [d] Chlorination product was obtained in 40% yield.

Next, the scope of silyl ketene acetals **1** was examined using **2a** (Table 2). Whereas the reaction of α-alkyl-substituted silyl ketene acetals was sluggish,[14] α-aryl-substituted

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(9) For transition-metal-catalyzed direct C–H amination with other electrophilic nitrogen sources, see: (a) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (b) Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhang, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1694. (c) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652. (d) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2860. (e) Liu, X.-Y.; Gao, P.; Shen, Y.-W.; Liang, Y.-M. *Org. Lett.* **2011**, *13*, 4196. (f) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110.

(10) (a) Horiike, M.; Oda, J.; Inouye, Y.; Ohno, M. *Agric. Biol. Chem.* **1969**, *33*, 292. (b) Oguri, T.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1975**, *23*, 167. See also: (c) Smulik, J. A.; Vedejs, E. *Org. Lett.* **2003**, *5*, 4187 and references therein.

(11) For reviews on α-amination of carbonyl compounds, see: (a) Greck, C.; Drouillat, B.; Thomassigny, C. *Eur. J. Org. Chem.* **2004**, 1377. (b) Erdik, E. *Tetrahedron* **2004**, *60*, 8747. (c) Ciganek, E. *Org. React.* **2008**, *72*, 1.

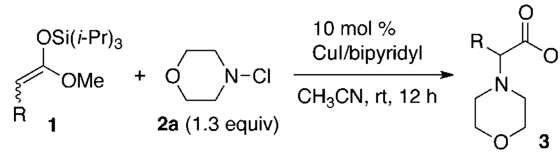
(12) Other copper catalysts such as CuCl, CuBr, Cu(OAc), CuCN, CuCl$_2$, Cu(acac)$_2$, and Cu(OAc)$_2$ gave inferior results.

(13) When *N*-benzoyloxymorpholine was used instead of *N*-chloromorpholine (**2a**) under the same reaction conditions, **3aa** was obtained in 80% yield.

(14) α-Methyl-substituted silyl ketene acetal gave the desired product in 23% yield.

substrates successfully participated in the reaction. All three substrates **1d**−**f** with isomeric tolyl substituents afforded the corresponding products **3da**−**fa** in good yields (entries 1−3). Both electron-withdrawing and -donating groups were allowed for the aryl substituent (entries 4−6). Thienyl-substituted substrate **1j** also gave the product **3ja** in 67% yield (entry 7).

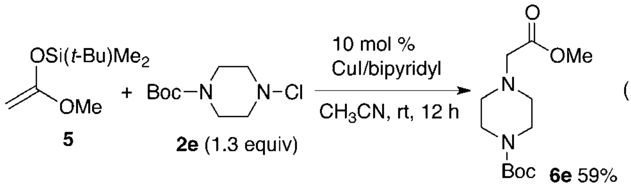
Table 2. Cu(I)-Catalyzed Amination Reaction of Various Silyl Ketene Acetals **1d**−**j** with 4-Chloromorpholine **2a**[a]



entry	**1** (R, *E*/*Z*)	**3**	yield (%)[b]
1	**1d** (4-MeC_6H_4, 84:16)	**3da**	83
2	**1e** (3-MeC_6H_4, 81:19)	**3ea**	79
3	**1f** (2-MeC_6H_4, 68:32)	**3fa**	70
4	**1g** (4-$MeOC_6H_4$, 87:13)	**3ga**	89
5	**1h** (4-$CF_3OC_6H_4$, 15:85)	**3ha**	55[c]
6	**1i** (4-ClC_6H_4, 45:55)	**3ia**	72
7	**1j** (3-thienyl, 58:42)	**3ja**	67

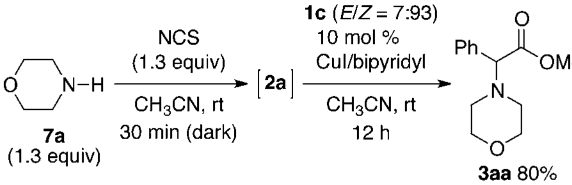
[a] Conditions: **1** (0.20 mmol), **2a** (0.26 mmol), CuI (10 mol %), and 2,2′-bipyridyl (10 mol %) in CH_3CN (2 mL) at rt for 12 h, unless otherwise noted. [b] Isolated yield. [c] Using 0.36 mmol of **2a**.

The commercially available *t*-butyldimethylsilyl ketene acetal **5** produced glycine derivative **6e** in 59% yield (eq 1).



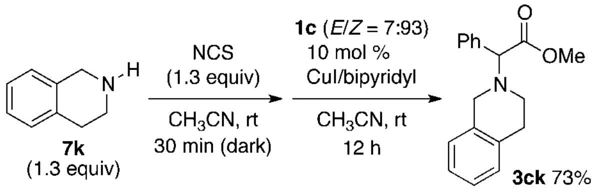
(1)

The facile availability of *N*-chloroamines from secondary amines permits a one-pot two-step synthesis starting from amines on gram scale (eq 2). Treatment of morpholine (**7a**, 0.68 g, 7.8 mmol) with *N*-chlorosuccinimide (NCS, 1.04 g, 7.8 mmol) in CH_3CN at room temperature for 30 min generated *N*-chloromorpholine (**2a**) quantitatively. Then, **1c** (1.85 g, 6.0 mmol), CuI (10 mol %), and 2,2′-bipyridyl (10 mol %) were sequentially added to the reaction mixture, which was further stirred at room temperature for 12 h. The product **3aa** (1.14 g, 4.8 mmol) was isolated in 80% yield based upon **1c**. The one-pot synthesis demonstrates another advantage from the practical standpoint.



(2)

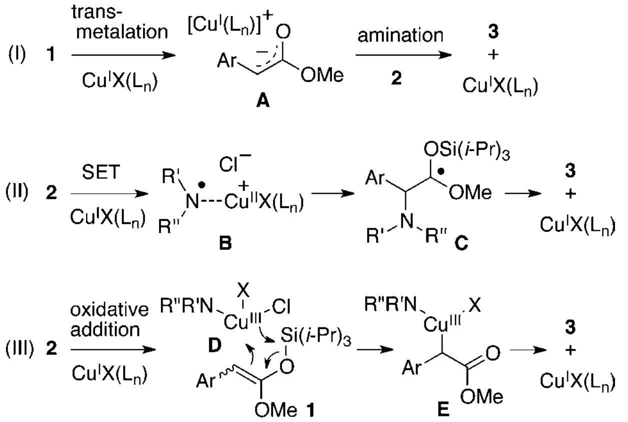
This one-pot two-step method was useful particularly when an *N*-chloroamine was too unstable to be isolated, as exemplified in eq 3.[15] The α-amino ester **3ck** was obtained in 73% yield directly from 1,2,3,4-tetrahydroisoquinoline (**7k**).



(3)

Upon the basis of experimental precedents in the literature, three plausible pathways are conceived for production of **3** from **1** and **2** (Scheme 2). In pathway (I), silyl ketene acetal **1** initially undergoes transmetalation[16] with copper(I) to generate nucleophilic copper(I) enolate **A**.[17] The following reaction with *N*-chloroamine **2** gives α-amino ester **3**. Pathway (II) involves single-electron transfer (SET) from copper(I) to *N*-chloroamine **2**.[18] The resulting aminyl radical intermediate **B** couples with silyl ketene acetal **1**. SET back to copper(II) produces α-amino ester **3** together with triisopropylchlorosilane and copper(I). In pathway (III), *N*-chloroamine **2** initially undergoes oxidative addition to copper(I) to generate amino copper(III) species **D**.[2h] Transmetalation with silyl ketene acetal **1** furnishes copper(III) enolate **E**, and reductive elimination ensues.

Scheme 2. Proposed Mechanisms for the Formation of **3** from **1** and **2**



Whereas a catalytic reaction of **1c** with **2a** using CuI/1,10-phenanthroline gave **3aa** in 72% yield, a stoichiometric reaction of **2a** with copper/1,10-phenanthroline enolate **A**, generated according to the Hartwig's procedure,

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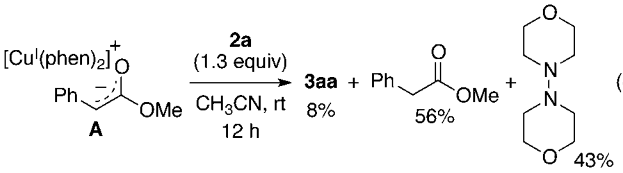
(15) When cyclohexylamine was treated with **1c** under the same one-pot reaction conditions, the desired α-amino ester was obtained in 20% yield.

(16) For transmetalation between Cu(I) and trimethylsilyl ketene acetals in the presence of a base, see: (a) Oisaki, K.; Suto, Y.; Kanai, M.; Shibsaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5644. (b) Li, D.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2011**, *133*, 5672.

(17) Huang, Z.; Hartwig, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 1028.

(18) (a) Heuger, G.; Kalsow, S.; Göttlich, R. *Eur. J. Org. Chem.* **2002**, 1848. (b) Tsuritani, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2003**, *68*, 3246.

yielded only 8% of **3aa** together with methyl phenylacetate (56% yield) and 4,4′-bimorpholine (43% yield based upon **2a**) (eq 4).



(4)

In addition, the reaction of **1c** with **2a** under the standard conditions but in the presence of TEMPO (1.0 equiv) afforded **3aa** in almost same yield (72%). Thus, we prefer pathway (III) as the most likely mechanistic scenario, albeit with no experimental evidence to support it.

In summary, we have developed a copper-catalyzed amination reaction of silyl ketene acetals with *N*-chloroamines under mild reaction conditions. This reaction provides an efficient synthetic route to α-amino esters, which are substructures found in a variety of bioactive compounds.

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Supporting Information Available. Experimental details and spectra data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.